MAY 25 2000

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 21-213	SUBMISSION DATE: 12-10-1999
BRAND NAME:	Mevacor CC (nonprescription lovastatin)
GENERIC NAME:	Lovastatin 10 mg tablets
REVIEWER:	Xiaoxiong (Jim) Wei, M.D., Ph.D.
SPONSOR:	Merck & Co., West Point, PA
TYPE OF SUBMISSION:	Original NDA for OTC

SYNOPSIS:

On December 10, 1999, Merck submitted NDA21-213 for Mevacor CC 10-mg tablets (nonprescription lovastatin). This supplement is an electronic submission.

The majority of the information presented in this submission is collection of material from the original lovastatin NDA, subsequent supplements and published articles after approval of the prescription lovastatin NDA. Only the information regarding the results of a multiple-dose study with 10- and 40-mg doses of lovastatin in healthy male subjects is submitted as "new information" in this current NDA. The 10-mg tablet of lovastatin proposed for the nonprescription market is the same composition, except for a slight change in coloring, as that currently marketed for prescription lovastatin.

The sponsor also included a complete in vivo study of grapefruit juice interaction with lovastatin, which had submitted to supplement NDA19-643 (SLR-059) in 06-24-99. The main goals of this review are to try to answer the following important questions:

1. Is 10 mg-Mevacor® CC proportional to 40-mg Mevacor® in pharmacokinetic profiles?
2. Does grapefruit juice have a minimal effect on lovastatin or is the interaction between grapefruit juice and lovastatin of no clinical relevance?
3. What are our safety concerns about 10 mg-Mevacor® CC from clinical pharmacology perspective?

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has reviewed NDA 21-213 OTC Mevacor® CC (nonprescription lovastatin) 10 mg tablets submitted on December 10, 1999. The labeling changes/comments (Page 8) and general comments (Page 9) should be sent to the sponsor as appropriate.

PROCESS
ORIGINAL REVIEW

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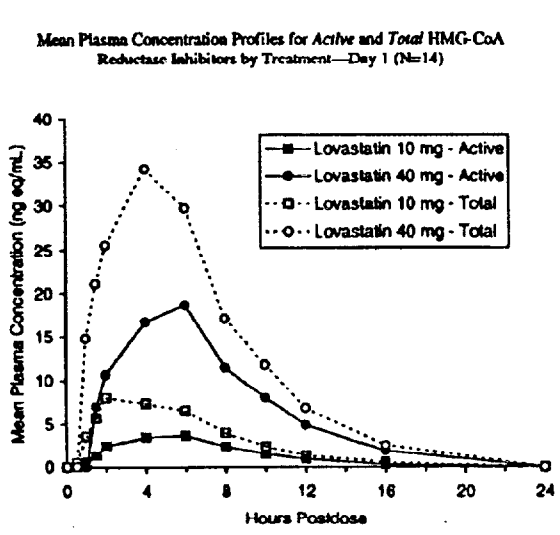
CLINICAL PHARMACOLOGY

1. Is 10 mg-Mevacor® CC proportional to 40-mg Mevacor® in pharmacokinetic profiles?

The sponsor conducted a new pharmacokinetic study (Protocol #82) to determine the plasma-concentration-time profile of lovastatin, lovastatin acid and 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitory activity following single and multiple oral dose administrations of 10 mg and 40 mg lovastatin to healthy male subjects. This was an open, randomized, multiple-dose, 2-period, crossover study. Each subject received 2 treatments (A and B): Treatment A—a single once-daily oral dose of lovastatin 10 mg for 10 days; Treatment B—a single once-daily oral dose of lovastatin 40 mg for 10 days. For both treatments, the lovastatin dose was administered on 10 consecutive evenings following a meal. Blood samples for pharmacokinetic measurements were taken for 24 hours following the Days 1 and 10 lovastatin dose. Treatment periods were separated by a washout period of at least 10 days.

The results are summarized in the Table 1 and Figure 1.

Figure 1:



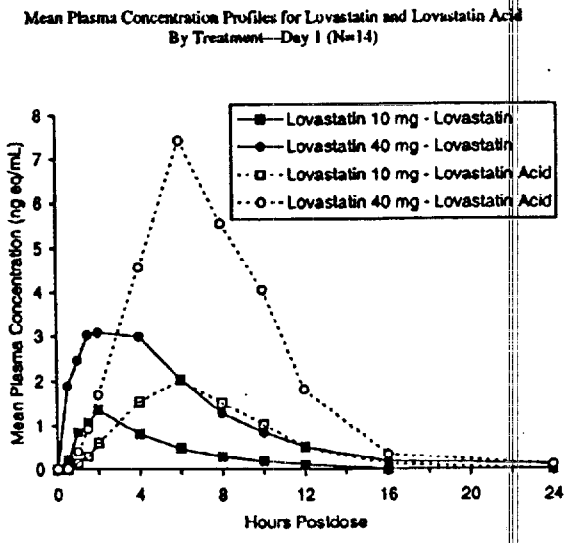


Table 1:

Lovastatin 10 mg (N=14)

Parameter	Study Day	HMG-CoA Reductase Inhibitors *Active* Mean	*Active* 90% CI	*Total* Mean	*Total* 90% CI	Lovastatin Mean	Lovastatin 90% CI	Lovastatin Acid Mean	Lovastatin Acid 90% CI
AUC (ng•eq•hr/mL)	Day 1	30.5	(24.2, 36.8)	63.3	(53.6, 73.0)	6.8	(5.6, 8.1)	15.5	(11.7, 19.3)
	Day 10	29.6	(24.7, 34.6)	67.4	(60.3, 74.4)	6.3	(5.3, 7.4)	13.0	(10.2, 15.7)
	Day 10/ Day 1†	1.0		1.1		1.0		0.9	
C_{max} (ng•eq/mL)	Day 1	4.9	(4.0, 5.8)	12.0	(9.9, 14.1)	1.7	(1.1, 2.4)	2.3	(1.8, 2.8)
	Day 10	5.2	(4.4, 6.0)	14.1	(12.2, 16.0)	1.7	(1.4, 2.1)	2.0	(1.6, 2.4)
T_{max} (hr)	Day 1	4.8	(3.8, 5.8)	3.6	(2.6, 4.6)	2.8	(1.9, 3.6)	5.4	(4.6, 6.2)
	Day 10	3.5	(2.5, 4.5)	2.5	(1.9, 3.0)	2.2	(1.6, 2.8)	5.1	(4.3, 5.9)
$t_{½}$ (hr)	Day 1					2.6‡			

† Geometric mean of AUC ratios (Day 10/Day 1).
‡ Harmonic mean.

Lovastatin 40 mg (N=14)

Parameter	Study Day	HMG-CoA Reductase Inhibitors *Active* Mean	*Active* 90% CI	*Total* Mean	*Total* 90% CI	Lovastatin Mean	Lovastatin 90% CI	Lovastatin Acid Mean	Lovastatin Acid 90% CI
AUC (ng•eq•hr/mL)	Day 1	155.8	(127.0,184.5)	276.4	(235.8,316.9)	25.0	(20.4, 29.7)	54.0	(42.5, 65.5)
	Day 10	159.6	(127.2,192.0)	297.7	(247.6,347.9)	26.5	(21.3, 31.8)	55.9	(41.8, 70.0)
	Day 10/ Day 1†	1.0		1.1		1.0		1.0	
C_{max} (ng•eq/mL)	Day 1	26.2	(22.0, 30.4)	50.5	(43.4, 57.6)	5.1	(3.6, 6.7)	8.8	(7.1, 10.5)
	Day 10	22.1	(18.7, 25.5)	48.7	(38.0, 59.3)	5.1	(3.5, 6.6)	7.8	(6.2, 9.5)
T_{max} (hr)	Day 1	5.1	(4.0, 6.2)	4.3	(3.2, 5.3)	3.4	(2.4, 4.3)	5.3	(4.3, 6.3)
	Day 10	5.4	(3.9, 6.9)	4.3	(2.8, 5.7)	3.5	(2.0, 5.0)	6.6	(5.5, 7.6)
$t_{½}$ (hr)	Day 1					2.8‡			

† Geometric mean of AUC ratios (Day 10/Day 1).
‡ Harmonic mean.

REVEWER'S COMMENTS:

This reviewer agrees with the sponsor's conclusion that 10-mg lovastatin is proportional to 40-mg lovastatin in this newly performed PK study (Protocol #82). There is no obvious accumulation after multiple dose administration for both doses in this new pharmacokinetic study. However, PK studies in the original NDA, which is reflected in labeling, indicate that with a once-a-day dosing regimen, plasma concentrations of total inhibitors achieved a steady state between the second and third days of therapy and were about 1.5 times those following a single dose. The sponsor needs to clarify this difference in PK characteristics.

2. Does grapefruit juice have a minimal effect on lovastatin or is the interaction between grapefruit juice and lovastatin of no clinical relevance?

In this submission, the sponsor re-submitted their in vivo grapefruit juice interaction with lovastatin (Merck Study Protocol #078). Therefore, the content in this section is identical to that appearing in the review for NDA 19-643 (SLR-059). This study is designed to support their claim that grapefruit juice has a minimal effect on lovastatin. In this single-dose, placebo-controlled, positive-controlled, four-period, crossover study (Merck Study Protocol #078), the sponsor investigated the effect of grapefruit juice on lovastatin and midazolam pharmacokinetics in healthy subjects. Midazolam was used as a positive control for grapefruit juice interactions.

In the study, subjects received 8 oz of regular-strength grapefruit juice or 8 oz of water together with a standard breakfast in the mornings of Days 1-4 and a single 40-mg oral dose of lovastatin with 250 mL of water) in the evening of Day 3. It is worthwhile noticing that the sponsor used a medium dose, 40-mg lovastatin (the recommended dose ranging from 10 to 80 mg per day), and 12 hours apart between the grapefruit juice consumption and the administration of lovastatin. The summary of changes in pharmacokinetic profiles is listed in the following table.

Table 1. Mean (±SD, n=16) Pharmacokinetic Parameter Values for Total and Active HMG-CoA Reductase Inhibitors, Lovastatin, Lovastatin Acid and Midazolam in Healthy Male Subjects Receiving 40-mg Lovastatin or 2-mg Midazolam with and without Grapefruit Juice

Treatment	AUC (ng eq•hr/mL)	Cmax (ng eq/mL)	Tmax (hr)
	Total Inhibitors		
With Grapefruit juice	336 ± 92	58.4 ± 13.8	2.7 ± 1.3
With Water	245 ± 68	44.3 ± 20.4	3.5 ± 1.9
Ratio (G/W)[a]	1.36	1.42	-
	Active Inhibitors		
With Grapefruit juice	198 ± 72	29.5 ± 7.4	3.5 ± 1.7
With Water	147 ± 50	23.6 ± 10.5	3.8 ± 1.8
Ratio (G/W)[a]	1.34	1.30	-
	Lovastatin		
With Grapefruit juice	51.5 ± 36.7	11.4 ± 7.1	2.2 ± 0.8
With Water	24.6 ± 10.3	5.2 ± 3.3	3.1 ± 1.8
Ratio (G/W)[a]	2.09	2.19	-
	Lovastatin Acid		
With Grapefruit juice	73.9 ± 35	10.8 ± 4.5	4.6 ± 1.8
With Water	46.3 ± 19.8	6.4 ± 2.2	5.4 ± 1.6
Ratio (G/W)[a]	1.60	1.65	-
	Midazolam		
With Grapefruit juice	56.8 ± 16.9	25.5 ± 6.9	0.5 ± 0.1
With Water	24.5 ± 11.3	11.5 ± 4.8	0.6 ± 0.3
Ratio (G/W)[a]	2.41	2.32	-

Figure 1. Mean (+S.D.) Plasma Concentration Profiles (N=15) for Lovastatin in Healthy Male Subjects Following a Single 40-mg Dose of Lovastatin Administered With (•) and Without (o) Daily Consumption of 'Regular-Strength' Grapefruit Juice.

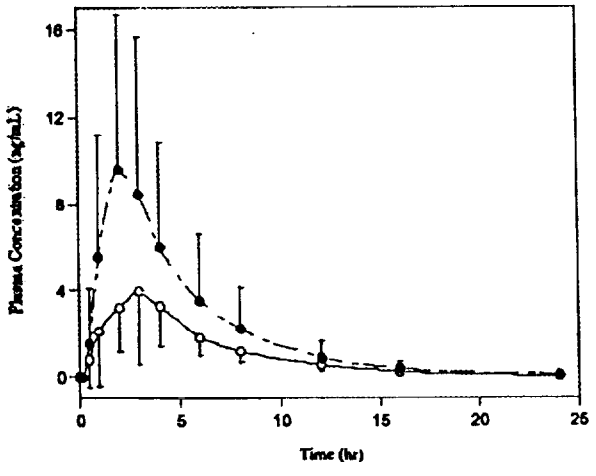
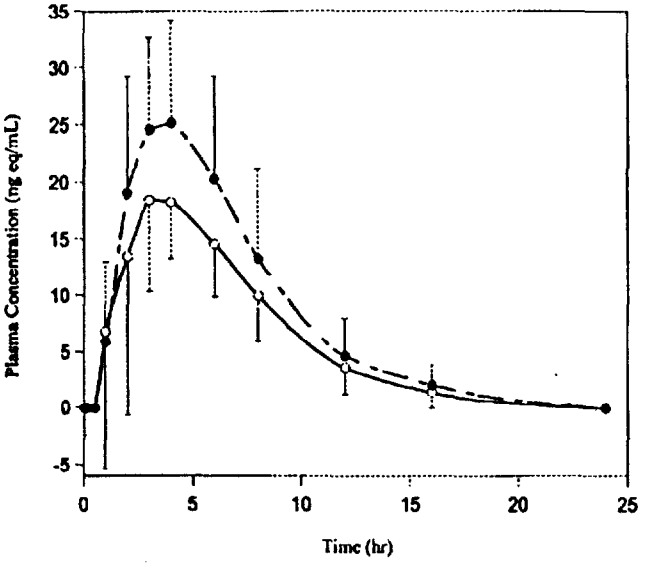


Figure 2. Mean (+S.D.) Plasma Concentration Profiles (N=15) of Active HMG-CoA Reductase Inhibitors in Healthy Male Subjects Following a Single 40-mg Dose of Lovastatin Administered With (•) and Without (o) Daily Consumption of 'Regular-Strength' Grapefruit Juice.



From the Table 1, we can see the increase in AUC is about 109% and 60% for lovastatin and lovastatin acid, respectively, although the consumption of grapefruit juice was 12 hour apart from the administration of lovastatin. The difference in AUC for active and total HMG-CoA reductase inhibitors is much less, only 34% and 36% increase, respectively. In later section, the rationale of using the active and total HMG-CoA reductase inhibitory activities as pharmacokinetic parameters will be discussed. The sponsor is trying to use these data to deliver their message that grapefruit juice has a minimal effect on lovastatin and there is no clinical relevance at all.

In this submission, the sponsor also collected major publications of studies on drug interactions with grapefruit juice. One of well-known articles is a paper entitled "Grapefruit juice greatly increases serum concentrations of lovastatin and lovastatin acid" by Kantola et al published in *the Journal of Clinical Pharmacology and Therapeutics* in 1998 (63(4): 397-402). In the study, 10 subjects took 200ml double-strength grapefruit juice or water three times a day for 2 days. On Day 3, each subject ingested 80 mg lovastatin with either 200 ml grapefruit juice or water in a randomized, 2 way crossover study design. Their data summary is listed as below:

Table 2. The PK parameters of lovastatin and lovastatin acid in 10 subjects after ingestion of 80 mg lovastatin with grapefruit juice or water.

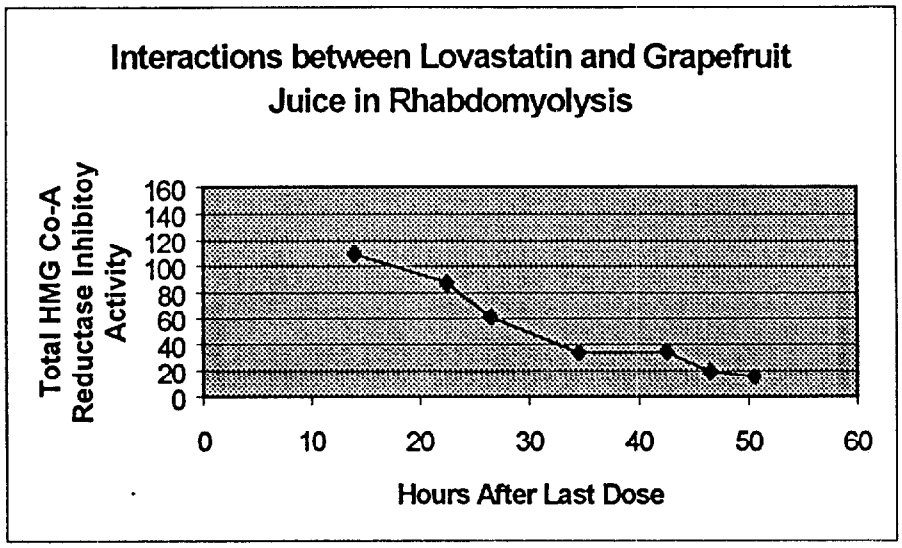
Treatment	AUC (ng eq•hr/mL)	Cmax (ng eq/mL)	Tmax (hr)	T1/2 (hr)
	Lovastatin			
With Grapefruit juice	429 ± 181	82.4 ± 39.6	3	3.0 ± 0.6
With Water	28.1 ± 9.7	7.0 ± 2.5	2	2.5 ± 0.6
Ratio (G/W)	15.3	11.8	1.5	1.2
	Lovastatin Acid			
With Grapefruit juice	384 ± 193	69.6 ± 36.3	5	2.5 ± 0.6
With Water	76.9 ± 44.5	17.6 ± 9.2	4	2.5 ± 1.1
Ratio (G/W)	5	4.0	1.25	1

It is clearly demonstrated that a large quantity of consumption of grapefruit juice drastically increased drug exposure (more than 15 folds increase in AUC for lovastatin).

Of the most important of all, a recent MedWatch report on rhabdomyolysis case has been analyzed and determined that rhabdomyolysis is related to grapefruit juice interaction with lovastatin. The key information of the MedWatch report is described below.

MedWatch #50227734 was submitted to NDA19-643 as a correspondence on January 11, 1999). It was reported that the patient was a 60-year-old man with diabetes mellitus, coronary heart disease, and chronic renal insufficiency, who had been treated for 5 to 10 years with lovastatin 40 mg twice daily and gemfibrozil 600 mg twice daily as well as several other medications. This patient presented with rhabdomyolysis after drinking grapefruit juice daily (8 ounces, ~250 mL) for 2 weeks while on vacation. Following discontinuation of these medication and grapefruit juice and a brief hospitalization, the patient recovered, except for a persistent creatinine elevation. It appears that grapefruit juice precipitated rhabdomyolysis in this patient. Fortunately, a series of blood samples were collected immediately after rhabdomyolysis diagnosed 14 hours after last dose of lovastatin (Figure 2). The sponsor explained that only the total HMG CoA reductase inhibitory activity was measured in this patient. In a correspondence to the Agency submitted in November 5, 1999, the sponsor estimated that the trough level of the total HMG CoA reductase inhibitory activity (109 ng.eq/ml) is about 10 times higher than the control level without confounding factors. After reviewing related data, this reviewer further estimated that the trough level of 109 ng.eq/ml is about 3 times the controls with confounding factors including renal impairment (2 folds) and multiple dosing (at least 1.5 folds of single dose) being considered.

Figure 3. The Series of Measurement of the Total HMG CoA Reductase Inhibitory Activity 14 hours after last 40-mg Lovastatin Dose.



Therefore, grapefruit juice can increase drug exposure of lovastatin to such a great extent that patients under lovastatin therapy can have an increased risk to develop rhabdomyolysis, which is the most severe and potentially fatal adverse drug event of statins.

REVEWER'S COMMENTS:

(1) Grapefruit juice increases lovastatin exposure in dose-dependent and time-dependent manners. Kantola's study and MedWatch report clearly demonstrate the risk of rhabdomyolysis when lovastatin is concomitantly administered with consumption of grapefruit juice.

(2) In Merck Study Protocol #78, there are major drawbacks in study design. Lovastatin dosing ranges from 10 to 80 mg per day. The single dose applied in the sponsor's study was 40 mg. The consumption of grapefruit juice and lovastatin administration was 12 hours apart. The maximal potential for grapefruit juice interaction may not have been seen. On the contrast, the positive control, midazolam was administered one hour after the consumption of grapefruit juice. Although the study design was to see the minimal potential of lovastatin interaction with grapefruit juice, the increase in AUC of lovastatin is still more than 2 folds.

3. What are our safety concerns about 10 mg-Mevacor® CC from clinical pharmacology perspective?

From clinical pharmacology perspective, the following facts concern us about safety of Mevacor® once it becomes available over the counter.

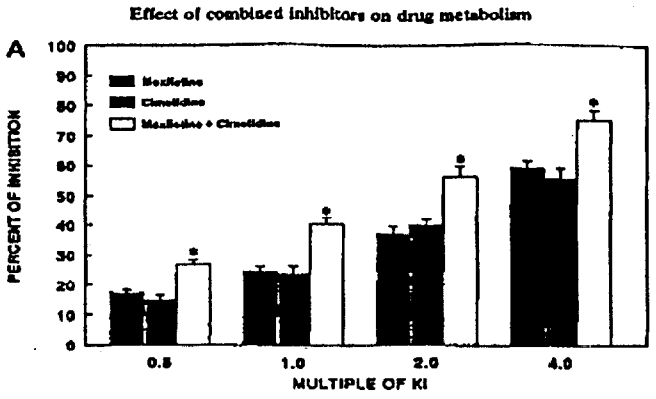
(1) CYP3A4 variability: In general, the CYP3A4 activity varies between 5 to 10 folds in population. However, some reports showed that the range of CYP3A4 content is from 10 to 100 folds. Genetic polymorphism and environmental factors contribute to the great variability of CYP3A4 activity. This variability leads to a great variable fate of CYP3A4 drugs. The spectrum of lovastatin and its metabolites may be different in patients with different CYP3A4 activity. Lovastatin may accumulate in patients with very low activity of CYP3A4. Some recent research articles suggest that parent compound may inhibit signal transduction of cell membrane to cause muscle cell death.

(2) Susceptibility of rhabdomyolysis: The mechanism of rhabdomyolysis is unknown. Rhabdomyolysis occurred in patients who took variable doses. This reviewer surveyed 320 severe myopathy or rhabdomyolysis cases reported to MedWatch for lovastatin. There are 161 cases in which the dose was specified. The percentage of dose distribution is summarized in the following table:

DOSE	CASES	PERCENT
20 mg	65	40 %
40 mg	20	12.5 %
60 mg	56	35 %
80 mg	20	12.5 %
TOTAL	161	100 %

From this table we can see that rhabdomyolysis can occur in variable doses. Although 10 mg per day is the lowest dose to be recommended in labeling, often the patients are given a starting dose of 20 mg a day. Susceptibility to develop rhabdomyolysis is variable in patients. It can occur with high doses as well as with low doses of lovastatin. Age, renal function, etc. as intrinsic factors contribute the susceptibility. In addition, when drugs are available over the counter, patients can take more than one pill per day although only one tablet per day is recommended in labeling.

(3) Multiple drug interactions: The patients who need to take lipid-lowering drugs are likely in advanced age. They are often under multiple drug therapies. In general, most in vivo drug interaction studies and package inserts only emphasize two drug interactions. In real medical practicing, particularly in geriatric medicine, we often face multiple drug interactions. The following figures from this reviewer's paper published in 1995 in *Biochemical Pharmacology* [49 (11): 1657 – 63, 1995] reveals that multiple drug interactions can be additive for inhibitory effect on test drugs in low range of doses in an in vitro human microsomal study.



The concerns about multiple drug interactions also include grapefruit juice. In the sponsor's study between grapefruit juice and lovastatin interaction, the consumption of grapefruit juice 12 hours before the administration of lovastatin can increase the AUC of lovastatin about 2 folds. The magnitude of interaction can be further increased if other CYP3A4 drugs such as calcium channel blockers that are not listed in labeling.

Substrate-substrate competition is one of common mechanisms for drug-drug interactions. We have to bear in mind that 60 –70% of all marketed drugs are through the metabolism of CYP3A4.

LABELING COMMENTS:

(~~Strikeout text~~ should be removed from labeling; Double underlined text should be added to labeling; ☛ indicates an explanation only and is not intended to be included in the labeling)

DO NOT use MEVACOR CC with grapefruit/grapefruit juice and the following medicines:

- erythromycin, or clarithromycin-Biaxin (for infections)
- ketoconazole-Nizoral, or itra(3onazole-Sporanox (for fungal infections)
- nefazodone-Serzone (for depression)
- cyclosporine (for immune suppression)
- protease inhibitors (for HIV/AIDS)

* other cholesterol-reducing drugs such as:
- niacin at daily doses of 500 mg or more, or gemfibrozi
- prescription statin drugs including: simvastatin-Zocor®, pravastatin-pravachol, fluvastatin-Lescol, atorvastatin-Lipitor, cerivastatin-Baycol, lovastatin-Mevacor®

☛ It is important that grapefruit juice is listed because of the wide consumption in general population. For details, please see general comments and labeling comments sent to the sponsor in NDA19-643 (SLR059) about grapefruit juice interactions with lovastatin,

COMMENTS (TO BE SENT TO THE SPONSOR):
This reviewer agrees with the sponsor's conclusion that 10-mg lovastatin is proportional to 40-mg lovastatin in this newly performed PK study (Protocol #82). There is no obvious accumulation after multiple dose administration for both doses in this new pharmacokinetic study. However, in PK studies in original NDA, which is reflected in labeling indicate that with a once-a-day dosing regimen, plasma concentrations of total inhibitors achieved a steady state between the second and third days of therapy and were about 1.5 times those following a single dose. The sponsor needs to clarify this difference in PK characteristics.

Xiaoxiong Wei 5/25/00

Xiaoxiong (Jim) Wei, M.D., Ph.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader

FT initialed by Hae-Young Ahn, Ph.D., Team Leader 5/26/00

CC: NDA 21-213 (orig.,1 copy), HFD-510 (Simoneau), HFD-850 (Lesko), HFD-870 (Wei, Ahn, Huang), CDR.

CPB Briefing (May 13, 2000): Larry Leskol, Paul Hepp, Shiew-Mei Huang, John Hunt, Hae-Young Ahn, Robert Shore, Steve Johnson, Sam Haidar, Arzu Selen, Emmanuel Fadiran, John Jenkins, Mary Parks, Margaret Simoneau.

Attached: study summary, proposed labeling.

MERCK RESEARCH LABORATORIES

CLINICAL STUDY REPORT
I. SYNOPSIS

MK-0803
Lovastatin
Conventional Tablets

PROTOCOL TITLE/NO.: An Open, Randomized, Multiple-Dose, Two-Period Crossover Study to Determine the Single and Multiple Dose Pharmacokinetics of Lovastatin at 10- and 40-mg Oral Doses in Healthy Male Subjects #082

INVESTIGATOR(S)/STUDY CENTER: Robert A. Blum, Buffalo, NY 14209-1194, U.S.A.

PRIMARY THERAPY PERIOD: 19-Feb-1999 to 20-Mar-1999. The in-house case report form cutoff date was 02-Aug-1999.

CLINICAL PHASE: I

DURATION OF TREATMENT: Two treatment periods of 10 days each.

OBJECTIVE(S): Primary: To determine the plasma-concentration-time profile of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitory activity and of lovastatin and lovastatin acid concentrations following single and multiple oral dose administration of 10 mg lovastatin to healthy male subjects. Secondary: To determine the plasma-concentration-time profile of HMG-CoA reductase inhibitory activity and of lovastatin and lovastatin acid concentrations following single and multiple oral dose administration of 40 mg lovastatin to healthy male subjects.

STUDY DESIGN: This was an open, randomized, multiple-dose, 2-period, crossover study. Each subject received 2 treatments (A and B): Treatment A—a single once-daily oral dose of lovastatin 10 mg for 10 days; Treatment B—a single once-daily oral dose of lovastatin 40 mg for 10 days. For both treatments, the lovastatin dose was administered on 10 consecutive evenings following a meal. Blood samples for pharmacokinetic measurements were taken for 24 hours following the Days 1 and 10 lovastatin dose. Treatment periods were separated by a washout period of at least 10 days.

SUBJECT ACCOUNTING:

ENTERED: Total	14
Male (age range)	14 (18 to 45)
Female (age range)	0
COMPLETED:	14
DISCONTINUED: Total	0

DOSAGE/FORMULATION NOS.: Treatment A = lovastatin 10-mg conventional tablet (CT) (H1196); Treatment B = lovastatin 40-mg CT (H9616)

DIAGNOSIS/INCLUSION CRITERIA: Healthy, nonsmoking men between 18 to 45 years of age.

EVALUATION CRITERIA: The pharmacokinetic parameters AUC, C_{max}, and T_{max} of *total* and *active* HMG-CoA reductase inhibitory activity and of lovastatin and lovastatin acid were calculated for each subject. In addition, the $t_{½}$ of lovastatin was calculated. AUC represents the area under the plasma-concentration-time profile; C_{max} represents the maximum plasma concentration, T_{max} represents the time at which the maximum plasma concentration was reached, and $t_{½}$ represents half-life. These pharmacokinetic parameters were computed after single and multiple evening oral doses of lovastatin 10 and 40 mg. Subjects were assessed for adverse experiences each period.

STATISTICAL PLANNING AND ANALYSIS: The primary aim of this study was to estimate the plasma-concentration-time profile of HMG-CoA reductase inhibitory activity and lovastatin and lovastatin acid concentrations after single and multiple dosing of lovastatin 10 and 40 mg. No formal hypotheses were specified for within- or between-treatment inferential testing. Instead, from an estimation standpoint, after single and multiple 10- and 40-mg dosing, 90% confidence intervals were computed for the mean of each of the pharmacokinetic parameters by treatment group. These confidence intervals were computed for the pharmacokinetic parameters for HMG-CoA reductase inhibitors and for lovastatin and lovastatin acid.

In an exploratory manner, the dose-adjusted AUC of HMG-CoA reductase *total* inhibitors for 10 mg was compared to the 40 mg AUC using an analysis of variance (ANOVA) model appropriate for a 2-treatment, 2-period crossover design. An additional exploratory summary of the data which was not described in the protocol was produced for individual and mean AUC ratios (Day 10/Day 1) for each of the pharmacokinetic parameters by treatment group.

RESULTS: Pharmacokinetics: All 14 randomized subjects completed the 2 study periods and all were included in the analyses. The 90% confidence intervals for the mean of each of the pharmacokinetic parameters after single and multiple dosing of lovastatin 10 and 40 mg are displayed in the following tables by treatment. The geometric mean of the individual AUC ratios (Day 10/Day 1) is also presented.

Lovastatin 10 mg (N=14)

Parameter	Study Day	HMG-CoA Reductase Inhibitors: *Active* Mean	*Active* 90% CI	*Total* Mean	*Total* 90% CI	Lovastatin Mean	Lovastatin 90% CI	Lovastatin Acid Mean	Lovastatin Acid 90% CI
AUC (ng•eq•hr/mL)	Day 1	30.5	(24.2, 36.8)	63.3	(53.6, 73.0)	6.8	(5.6, 8.1)	15.5	(11.7, 19.3)
	Day 10	29.6	(24.7, 34.6)	67.4	(60.3, 74.4)	6.3	(5.3, 7.4)	13.0	(10.2, 15.7)
	Day 10/ Day 1†	1.0		1.1		1.0		0.9	
C_{max} (ng•eq/mL)	Day 1	4.9	(4.0, 5.8)	12.0	(9.9, 14.1)	1.7	(1.1, 2.4)	2.3	(1.8, 2.8)
	Day 10	5.2	(4.4, 6.0)	14.1	(12.2, 16.0)	1.7	(1.4, 2.1)	2.0	(1.6, 2.4)
T_{max} (hr)	Day 1	4.8	(3.8, 5.8)	3.6	(2.6, 4.6)	2.8	(1.9, 3.6)	5.4	(4.6, 6.2)
	Day 10	3.5	(2.5, 4.5)	2.5	(1.9, 3.0)	2.2	(1.6, 2.8)	5.1	(4.3, 5.9)
$t_{½}$ (hr)	Day 1					2.6‡			

† Geometric mean of AUC ratios (Day 10/Day 1).
‡ Harmonic mean.

Lovastatin 40 mg (N=14)

Parameter	Study Day	HMG-CoA Reductase Inhibitors: *Active* Mean	*Active* 90% CI	*Total* Mean	*Total* 90% CI	Lovastatin Mean	Lovastatin 90% CI	Lovastatin Acid Mean	Lovastatin Acid 90% CI
AUC (ng•eq•hr/mL)	Day 1	155.8	(127.0, 184.5)	276.4	(235.8, 316.9)	25.0	(20.4, 29.7)	54.0	(42.5, 65.5)
	Day 10	159.6	(127.2, 192.0)	297.7	(247.6, 347.9)	26.5	(21.3, 31.8)	55.9	(41.8, 70.0)
	Day 10/ Day 1†	1.0		1.1		1.0		1.0	
C_{max} (ng•eq/mL)	Day 1	26.2	(22.0, 30.4)	50.5	(43.4, 57.6)	5.1	(3.6, 6.7)	8.8	(7.1, 10.5)
	Day 10	22.1	(18.7, 25.5)	48.7	(38.0, 59.3)	5.1	(3.5, 6.6)	7.8	(6.2, 9.5)
T_{max} (hr)	Day 1	5.1	(4.0, 6.2)	4.3	(3.2, 5.3)	3.4	(2.4, 4.3)	5.3	(4.3, 6.3)
	Day 10	5.4	(3.9, 6.9)	4.3	(2.8, 5.7)	3.5	(2.0, 5.0)	6.6	(5.5, 7.6)
$t_{½}$ (hr)	Day 1					2.8‡			

† Geometric mean of AUC ratios (Day 10/Day 1).
‡ Harmonic mean.

Safety: There were no serious clinical, laboratory, or other adverse experiences and no subjects died during the study. Overall, 12 of 14 subjects had clinical adverse experiences, of which 1 subject (40-mg CT) had an adverse experience that was regarded as possibly drug related. Four of 14 subjects had laboratory adverse experiences, of which none were regarded as drug related.